

The different effects of sodium bicarbonate and aluminium hydroxide on the absorption of indomethacin in man

J. C. GARNHAM
M.B., B.S.

T. KASPI

C. M. KAYE
Ph.D.

V. M. S. OH
M.R.C.P.

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

Summary

The influence of oral sodium bicarbonate and aluminium hydroxide on the absorption of indomethacin has been studied in normal volunteers. While sodium bicarbonate appeared to increase indomethacin absorption, aluminium hydroxide markedly reduced both the rate and extent of absorption. The buccal absorption of indomethacin over the pH range 5-9 was also studied in normal volunteers, and showed that the percentage absorption increased markedly as the pH was reduced. The clinical importance both of pH-partition and of adsorption are discussed in the context of antacid interactions. It is concluded that caution must be exercised when prescribing an antacid with other orally-administered drugs.

Introduction

Various anti-inflammatory agents such as aspirin and indomethacin are frequently taken over the same period by the same patient (Mason *et al.*, 1975). Furthermore, antacids are sometimes added to the therapeutic regimen to relieve the dyspepsia caused by such drugs. The effect of these compounds on each other has been the subject of several studies (Champion *et al.*, 1972; Jeremy and Towson, 1970; Garnham *et al.*, 1975).

Garnham *et al.* (1973) suggested that not only the nature of the companion drug, but also the relative timing of the administration of the two drugs might be important, furthermore 'concurrent' is not necessarily the same as 'simultaneous' administration of a drug.

In a recent paper, Brooks *et al.* (1975) examined the effect of the concurrent administration of soluble aspirin on plasma indomethacin levels. They used a partly buffered aspirin with a formulation different from the aspirin formulations used in the other studies (Champion *et al.*, 1972; Jeremy and Towson, 1970; Garnham *et al.*, 1975). They achieved similar results to those of Champion *et al.* in 1972.

Reprint requests to Dr V. Oh.

Garnham *et al.* (1975) postulated that it was the addition of the antacid to aspirin and the simultaneous administration of the buffered aspirin that increased the rate of absorption of indomethacin found by the present authors. This paper describes studies to evaluate the passage of indomethacin alone—a weak acid—across mucous membranes by the buccal absorption test (Becket and Triggs, 1967) at different pHs and the absorption of indomethacin into the blood stream after oral administration alone and together with two different antacids.

Subjects and methods

The influence of two antacids on the absorption of indomethacin (Indocid) was studied in six healthy volunteers (one female and five male) aged 19-31 years none of whom had a history of gastrointestinal disease. The three treatments (indomethacin 50 mg plus sodium bicarbonate 1400 mg as an aqueous solution, and indomethacin 50 mg plus aluminium hydroxide 700 mg as an aqueous suspension and indomethacin 50 mg alone) were administered orally at weekly intervals according to a balanced, randomized design. On the fourth week all six subjects received a further treatment (indomethacin 50 mg plus sodium bicarbonate tablets 600 mg). On each occasion the subjects had fasted overnight and venous blood samples were obtained before, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hr after dosing. Plasma concentrations of indomethacin were measured fluorimetrically by a method based on that described by Hvidberg, Lausen and Jansen (1972). Student's paired *t*-test was used for statistical analysis.

The buccal absorption of indomethacin over the pH range 5-9 was studied in eight healthy volunteers according to the method of Becket and Triggs (1967). The indomethacin remaining in the diluted saliva was determined by ultra-violet spectrophotometry after using the double extraction method of Hvidberg *et al.* (1972).

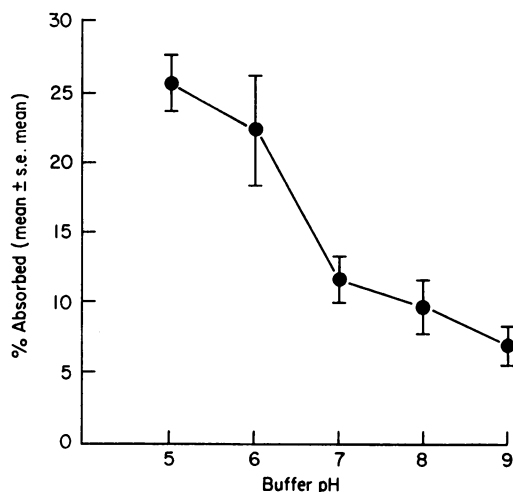


FIG. 1. The influence of pH on the buccal absorption of indomethacin.

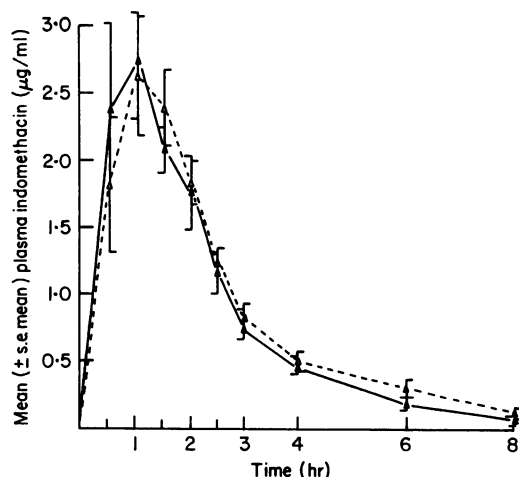


FIG. 3. Plasma levels of indomethacin in six healthy volunteers after 50 mg oral dose with sodium bicarbonate in tablet form (Δ --- Δ) and in aqueous solution (\blacktriangle — \blacktriangle).

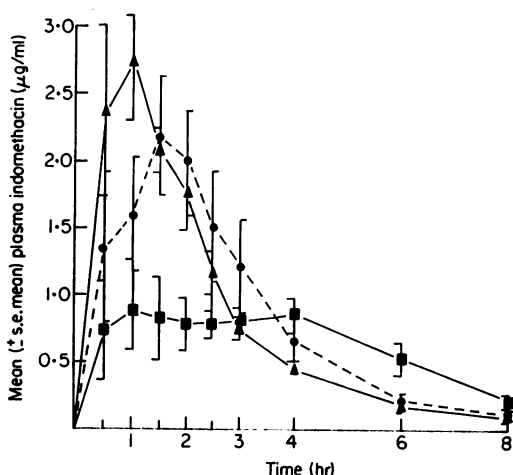


FIG. 2. Plasma levels of indomethacin in six healthy volunteers after 50 mg oral indomethacin alone (\bullet --- \bullet), with sodium bicarbonate (\blacktriangle — \blacktriangle) and with aluminium hydroxide (\blacksquare — \blacksquare).

Results

The mean (\pm s.e. mean) results of the eight volunteers who took part in the buccal absorption study are shown in Fig. 1. As predicted from theoretical considerations the absorption of indomethacin decreased as the pH was increased from 5 to 9. The mean (\pm s.e. mean) results of the six volunteers who took part in the study involving the two antacids are shown in Figs 2 and 3. The mean plasma levels shown in Fig. 2 demonstrate that aluminium hydroxide reduces the rate of absorption of indomethacin, the differences between the corresponding

plasma levels being statistically significant at 1.5 and 2 hr. It would appear that sodium bicarbonate increases the rate of absorption of indomethacin leading to somewhat higher and earlier peak plasma levels although, owing to inter-individual variation, the differences between the corresponding levels at 30 and 60 min just failed to attain statistical significance. However, Fig. 2 clearly shows that the two antacids, sodium bicarbonate and aluminium hydroxide, have markedly different effects on the absorption of indomethacin, the differences between the corresponding plasma levels being statistically significant at 0.5, 1, 1.5, 2, 6 and 8 hr. Figure 3 compares the effects of sodium bicarbonate taken in solution or as tablets on the absorption of indomethacin. As can be seen, the mean plasma level profiles are almost identical and reflect the very little intra-subject variation found, under similar conditions.

Discussion

The buccal absorption test showed that, at different pHs, the passage of indomethacin across a mucous membrane in an uncomplicated situation is exactly what would be predicted from the pH partition hypothesis, i.e. at low pHs where there is less dissociation, absorption is greatest (see Fig. 1). However, the rest of the data show how dangerous it is to extrapolate from the simple situation in the mouth with the drug in solution to the complicated situation further along the gastro-intestinal tract with the drug in a capsule. One might expect antacids to decrease absorption of indomethacin and apparently aluminium hydroxide does that. However, there is a

large difference between the effect of aluminium hydroxide and that of sodium bicarbonate (see Fig. 2) which is significant at 0.5, 1, 1.5, 2, 6 and 8 hr. Whereas aluminium hydroxide decreases the rate of absorption, sodium bicarbonate, if anything, increases the rate of absorption of indomethacin. It is possible that the aluminium hydroxide adsorbs the indomethacin, or that indomethacin might form an insoluble aluminium salt derived from the soluble aluminium salts generated by the interaction of the hydroxide with the gastric acid. Khalil (1974) has shown that a suspension of 6.2% aluminium hydroxide dried gel produced a marked reduction in the digoxin content from a paediatric elixir, as did magnesium trisilicate. He also showed (El-Masry and Khalil, 1974) that atropine and hyoscine are adsorbed by magnesium trisilicate and belladonna mixture. Ambre and Fischer (1973) found that while aluminium hydroxide gel decreased the absorption of bishydroxycoumarin, magnesium hydroxide increased it.

It is sometimes said that gastric activity is such that large amounts of antacids must be given to have any effects. Kuna (1964) showed that six out of every twelve normal subjects had gastric juice with a pH of 5.5 or higher. In addition, 1,552 recordings of the pH values in 312 subjects showed only 19% to be in the 'free acid' pH range while 45% were in a pH range of 3.5–6.0.

Levin, Kirsner and Palmer (1951) in morning aspirations found that 45% of normal males and 60% of normal females had periods of 'anacidity'. James and Pickering (1949) found that sixteen of twenty-three patients showed pH values near neutral during sleep. Small amounts of antacids under these conditions could thus have marked effects on the pH. Garnham *et al.* (1975) showed that whereas one Bufferin tablet had only a slight effect on 50 ml N/10 hydrochloric acid, with N/100 hydrochloric acid an equilibrium of about pH 6 was obtained. Although the administration of acids or alkalis has been claimed to affect not only absorption but metabolism and/or excretion (Hurwitz and Sheenan, 1971; Andrews and Cornatzer, 1944; Hurwitz, 1971) as well, the effects seen in this experiment occur so early that it is likely they are predominantly due to effects on absorption. This is similar to the studies by Segre *et al.* (1974).

It is clear, therefore, that caution must be exercised in the interpretation of comments such as that by Emori *et al.* (1973) 'Antacid delays by 50% but does not diminish peak levels' (of indomethacin by aluminium hydroxide gel). Impressions gained from the literature of the effect of one class of drugs upon another may also have to be revised, for example, that antacids decrease the absorption of coumarin anticoagulants (Anonymous, 1967; Azarnoff and

Hurwitz, 1970; Hussar, 1970; McCallister, Chin and Lach, 1970).

When predicting the possible interaction between antacid preparations and other drugs, at least six possible factors should be considered:

(1) The solubility of the parent compound. Acidic drugs are more soluble at higher pHs and dissolution may thus be favoured.

(2) Ionization increases, in the case of an acidic compound, as the pH rises, thus reducing its passage across a mucous membrane, according to the pH partition hypothesis.

(3) The adsorbing or chelating ability of the antacid preparation.

(4) Physical interference, such as the effect of a viscous gel on the rate of disintegration of the drug's formulation.

(5) The buffering capacity of some antacids is higher than that of others.

(6) The rate of gastric emptying may vary at different gastric pH values.

Acknowledgments

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